

Supplementary Table 1. Summary of baseline biopsy data

Patient	Details	ER (%)	ER strength	PR (%)	PR strength	BCL-2 (%)	BCL-2 strength	Ki-67 (%)
	0 = archival 1 = fresh		0 = none 1 = weak 2 = mod 3 = strong		0 = none 1 = weak 2 = mod 3 = strong		0 = none 1 = weak 2 = mod 3 = strong	
01-001	1	95	3	95	3	100	3	10
01-004	0	80	3	60	3	90	3	5
01-005	0	90	3	90	3	90	3	20
01-006	0	90	3	80	3	90	3	20
01-007	0	90	3	80	3	95	3	30
01-008	0	90	3	10	3	90	3	10
01-009	0	90	3	90	3	100	3	5
01-010	0	90	2	0	0	80	2	5
01-011	0	100	3	100	3	95	3	30
01-012	0	100	3	2	1	100	2	15
01-013	1	95	3	95	3	95	3	5
01-014	0	80	2	50	2	90	3	15
01-015	0	80	2	100	3	50	2	1
02-001	0	90	3	90	3	100	3	10
02-002	0	90	3	3	1	70	2	10
01-016	1	100	3	0	0	90	3	30
01-017	0	90	3	30	3	90	3	ND
01-018	0	80	3	90	3	90	3	40
01-019	1	90	3	0	0	100	3	20
01-020	1	80	3	0	0	80	3	60
01-021	1	80	2	5	1	90	2	5
01-022	1	90	3	90	3	90	3	30
01-023	1	90	3	5	2	80	3	55
01-024	1	90	3	70	3	90	3	20
01-025	1	90	3	25	3	90	3	50
01-026	0	90	3	30	2	90	3	10
01-027	1	95	3	5	1	90	3	30
01-028	1	90	3	90	3	90	3	10
01-029	1	80	3	70	3	90	3	10
01-030	1	70	3	10	2	100	3	50
01-031	1	70	3	0	0	90	3	40
01-032	1	92	3	1	1	95	2	ND
01-033	1	90	3	0	0	90	3	10

Abbreviation: ND, not done.

Supplementary Table 2. Summary of previous breast cancer therapy

Patient	Adjuvant endocrine therapy	Adjuvant chemotherapy	Metastatic endocrine therapy	Metastatic chemotherapy or targeted therapy
01-001	None	None	None	None
01-004	None	None	Letrozole/palbociclib	None
01-005	Tamoxifen	AC	Letrozole	Nab-paclitaxel
01-006	Letrozole	ddAC (2 cycles)	Tamoxifen	Nab-paclitaxel
01-007	None	None	None	None
01-008	Tamoxifen	None	Letrozole, exemestane, everolimus	Nab-paclitaxel
01-009	Tamoxifen	AC	Anastrozole	None
01-010	Toremifene	CMF	Letrozole, tamoxifen, exemestane	Capecitabine, vinorelbine, liposomal doxorubicin
01-011	None	None	Anastrozole	None
01-012	Tamoxifen	None	Anastrozole, exemestane/everolimus	Nab-paclitaxel, doxorubicin, capecitabine, liposomal doxorubicin
01-013	None	None	None	None
01-014	Anastrozole	FEC-D (NAC)	Letrozole, tamoxifen, exemestane/everolimus	None
01-015	Tamoxifen	None	Letrozole, tamoxifen, exemestane/everolimus	Capecitabine, vinorelbine, liposomal doxorubicin
02-001	Tamoxifen, anastrozole	AC	Letrozole, tamoxifen, exemestane/everolimus	None
02-002	Tamoxifen	CMF	Letrozole/palbociclib, exemestane, anastrozole, tamoxifen, fulvestrant	None
01-016	Anastrozole	None	None	None
01-017	None	CMF	Letrozole, tamoxifen, exemestane	None
01-018	Tamoxifen	None	Letrozole, anastrozole, tamoxifen, exemestane/everolimus, toremifene, megestrol, fulvestrant	Capecitabine
01-019	Tamoxifen, letrozole	None	None	None
01-020	Tamoxifen, anastrozole	FEC	Exemestane	Paclitaxel, capecitabine
01-021	Tamoxifen, anastrozole	AC	None	None
01-022	Anastrozole	None	None	None
01-023	Anastrozole	AC-Docetaxel	Exemestane	Alpelisib (BYL719)
01-024	Tamoxifen	CMF	Letrozole	None
01-025	Tamoxifen	FEC-D	None	Carboplatin/paclitaxel + veliparib
01-026	None	None	Anastrozole	None
01-027	Tamoxifen	AC-TH (for unrelated HER2+ breast tumor)	Exemestane/everolimus	Abraxane
01-028	None	None	None	None
01-029	None	None	None	None
01-030	Tamoxifen	TC	Letrozole/palbociclib	None
01-031	Anastrozole	None	None	None
01-032	Anastrozole, tamoxifen, exemestane	FEC	None	None
01-033	Tamoxifen, letrozole, exemestane	None	Anastrozole, letrozole/palbociclib	Capecitabine

Abbreviations: dd, dose dense; NAC, neoadjuvant chemotherapy.

Supplementary Table 3. Treatment related adverse events reported in at least 10% of patients

Adverse event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)
Decreased WCC	12 (36)	14 (42)	3 (9)	0 (0)	29 (88)
Lymphopenia	9 (27)	10 (30)	9 (27)	1 (3)	29 (88)
Neutropenia	14 (42)	8 (24)	2 (6)	0 (0)	24 (73)
Nausea	17 (52)	5 (15)	0 (0)	0 (0)	22 (67)
Anemia	8 (24)	3 (9)	2 (6)	0 (0)	13 (39)
Thrombocytopenia	10 (30)	1 (3)	0 (0)	0 (0)	11 (33)
Vomiting	10 (30)	1 (3)	0 (0)	0 (0)	11 (33)
Diarrhea	5 (15)	2 (6)	2 (6)	0 (0)	9 (27)
Infection (any)	0 (0)	6 (18)	3 (9)	0 (0)	9 (27)
Fatigue	3 (9)	3 (9)	0 (0)	0 (0)	6 (18)
Lethargy	3 (9)	1 (3)	0 (0)	0 (0)	4 (12)
Pruritis	3 (9)	1 (3)	0 (0)	0 (0)	4 (12)
Rash	4 (12)	0 (0)	0 (0)	0 (0)	4 (12)

Abbreviations: WCC, white cell count.

Supplementary Table 4A. Response rate according to line of therapy

Variable	<i>De novo</i> & 1st line n = 11	2nd & 3rd line n = 10	≥ 4th line n = 12
Best overall response, n (%)			
Complete (CR)	0 (0)	0 (0)	1 (8)
Partial response (PR)	9 (82)	3 (30)	3 (25)
Stable disease (SD)	1 (9)	2 (20)	4 (33)
Progressive disease (PD)	1 (9)	5 (50)	4 (33)
Clinical benefit rate 24 wks (CBR)	10 (91)	5 (50)	8 (67)

Supplementary Table 4B. Response rate according to prior endocrine therapy

Variable	Prior tamoxifen* n = 21	Prior AI + CDK4/6 inhibitor# n = 4	Prior everolimus + exemestane# n = 7
Best overall response, n (%)			
Complete (CR)	1 (5)	1 (25)	0 (0)
Partial response (PR)	7 (33)	1 (25)	1 (14)
Stable disease (SD)	5 (24)	2 (50)	4 (57)
Progressive disease (PD)	8 (38)	0 (0)	2 (29)
Clinical benefit rate 24 wks (CBR)	13 (62)	4 (100)	5 (71)

* Prior tamoxifen therapy in the adjuvant (13), metastatic (4) or adjuvant and metastatic (4) setting

Prior therapy for metastatic disease

Supplementary Table 5. List of genes screened by ctDNA.

Gene	Amplicons	Gene	Amplicons
RB1	10	PTEN	16
FOXA1	4	BRAF	1
BRCA2	10	PIK3CA	21
ERBB2	9	TP53	17
KRAS	3	NF1	9
CDKN2A	4	KMT2D	5
CBFB	6	BRCA1	10
APC	10	NCOR1	17
CDH1	24	MED12	8
EGFR	14	MLL3 (KMT2C)	17
SF3B1	2	ATM	11
ESR1	10	ARID1A	14
PIK3R1	11	RUNX1	7
AKT1	2	SETD2	9
AKT2	1	ATR	7
CDKN1B	5	ARID1B	7
GATA3	18	ARID2	4
MAP2K4	11	BAP1	4
MAP3K1	43	CASP8	11
TBX3	2		

*The breast cancer primer panel covered 39 genes using 394 amplicons